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EDITORIAL COMMENT

Putting creatinine and hemoconcentration in their place as prognostic predictors in the conundrum of acute heart failure

Assentar a creatinina e a hemoconcentração no lugar correto enquanto preditores prognósticos na insuficiência cardíaca aguda

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''Homage to thee, O my heart! Homage to you, O my kidneys!''

The Egyptian Book of the Dead[a]

Many centuries ago, traditional Chinese medicine – today, quite rightly, a subject of some controversy in the Portuguese medical community – described a disorder termed ''heart and kidney failing to link,'' suggesting a close connection between dysfunction of the kidneys and of the heart. These may have been the first references to what is now known as cardiorenal syndrome (CRS), a complex ''disorder of the heart and the kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other''.[1–3]

Five subtypes of CRS are now recognized, but in all of them, both organs (heart and kidneys) show or develop structural and/or functional alterations.[4,5] Type 1 (acute CRS) – the subject of this editorial – refers to acute worsening of heart function leading to acute kidney injury (AKI) and/or dysfunction,[1–3] and can be found in 19-45% of patients with acute decompensated heart failure (ADHF) presenting with AKI.[4] AKI mostly occurs early, within 3-5 days of hospitalization, and appears to be a predictor of even worse prognosis, associated with higher short- and long-term all-cause and cardiovascular mortality and prolonged hospitalization. The well-documented risk factors for AKI in the context of AHF are a history of diabetes, severity of cardiac dysfunction on admission, use of high-dose diuretics (particularly loop diuretics, but also thiazides), vasodilator therapy, and use of larger radiocontrast volumes.[4]

The clinical presentation of type 1 CRS usually includes rapid worsening renal function (WRF) (suggestive of altered renal perfusion, unless proven otherwise), resulting in volume overload with signs and symptoms of fluid retention, pulmonary rales and systemic congestion, less frequently in low cardiac output with peripheral hypoperfusion, and in poor response to diuretics.[2,4,5] It should be borne in mind that in the context of AHF diuretic resistance is multifactorial and includes, in varying degrees, impaired renal blood flow, altered drug reabsorption, reduced glomerular filtration, low albumin concentrations, and increased levels of urea nitrogen and other organic acids competitively impeding diuretic availability at the site of action.[6,7] Ideally, in order to recognize renal dysfunction and to stratify the severity of AKI, the risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) and Acute Kidney

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[a] Eknoyan G. The kidneys in the Bible: what happened? J Am Soc Nephrol. 2005;16(12):3464-71.

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Injury Network (AKIN) classifications should be applied. The former is based on changes in serum creatinine (SCr) or glomerular filtration rate (GFR) and/or urine output, and is a good predictor of AKI severity and outcome. The AKIN classification is a modified adaptation of RIFLE, and can increase the sensitivity and specificity of AKI diagnosis. Although clinically available biomarkers are sometimes inadequate for a diagnosis of CRS and detection of AKI in ADHF, in clinical practice the suspicion of type 1 CRS derives from an increase in SCr and blood urea nitrogen (BUN).

BUN is a serum by-product of protein metabolism and is probably one of the oldest short- as well as long-term prognostic markers in patients with heart failure. In the Acute Decompensated Heart Failure National Registry (ADHERE) database, BUN $\geq$43 mg/dl was the single best predictor, followed by systolic blood pressure <115 mmHg on admission and SCr $\geq$2.75 mg/dl (243.1 μmol/l), of in-hospital mortality among 65 275 AHF admissions. These findings have been replicated in other studies and BUN levels should be measured in routine prognostic assessment of ADHF.[8] Creatinine is a breakdown product of creatine phosphate in muscle tissue, and increases in the blood when GFR decreases, an indication of renal dysfunction. Increases in SCr elevations are also associated with worse outcomes in heart failure patients, and are a strong independent predictor of both one- and five-year mortality.[8]

However, as Martins et al.[9] note in this issue of the *Journal*, an increase of SCr in AHF patients does not always imply renal dysfunction or worse prognosis. As the authors point out, AHF patients with mild creatinine elevation but without established renal failure have a better prognosis, since these changes are due to hemoconcentration (HC) rather than to true WRF. It should be noted that in this case, HC arises from an absolute or relative loss of water from blood plasma (deshydremia). In Martins et al.'s paper, HC was defined as an increase in hemoglobin during hospital stay, estimated by subtracting hemoglobin at discharge from hemoglobin at admission; a similar definition has been used by other investigators.[10–14] In their study, as in others, HC was associated with a better prognosis in patients with or without WRF, acting as a surrogate for anticongestive therapy, and had prognostic value in AHF patients without CKD but with elevated SCr. It would therefore be a mistake to argue that a simple increase in SCr indicates AKI, and in fact when associated with HC[3] – with no renal failure or chronic kidney disease – it is associated with better prognosis and survival. Such cases should be reclassified as 'pseudo-WRF'.

On the whole, the article by Martins et al. is clear, credible and well researched, with an accurate and judicious description of its limitations: its single-center and retrospective nature, the importance of missing data such as SCr and left ventricular ejection fraction, and the fact that pharmacological therapy at discharge was not recorded (with possible effects on prognosis).

Diuretics (mainly, but not only, loop diuretics) are the cornerstone of ADHF and CRS treatment. They relieve renal venous congestion and fluid overload and improve patients' symptoms and comfort, and their early use in severe ADHF can reduce mortality.[5,6] However, they are a double-edged sword: they may worsen kidney function and trigger even more neurohormonal systems. The use and effects of diuretic therapy must therefore be carefully monitored.[5,6] HC may be linked with increased risk of WRF during hospitalization, increased diuretic doses, and greater weight loss.[15] However, in multivariate analysis, HC is not linked with mortality, and an early increase (in the first week) in hemoglobin is independently associated with a favorable outcome, despite a slight worsening of renal function.[16]

Future research needs to focus on the differences between and determinants of late and early HC in AHF and to determine the cutoffs between them – because, apparently, only late HC is associated with improved survival[10] – and, bearing in mind that HC can be a surrogate for successful decongestion in AHF, to clarify why in some patients there is a conflict between HC and clinical assessment of venous congestion, with persistent congestion at discharge linked with increased mortality that is not HC-dependent. Finally, as Martins et al. suggest, HC is associated with better outcomes but cannot replace clinical assessment in the initial diagnosis of AHF and a proper diagnostic workup that includes specific biomarkers, as well as BUN, SCr, hemoglobin and hematocrit. In the meantime, all patients with AHF should promptly start pharmacological and non-pharmacological treatment in parallel, as recommended in the most recent guidelines.[5,6]

Conflicts of interest

The author has no conflicts of interest to declare.

References

1. Ronco C, Haapio M, House AA, et al. Cardiorenal syndrome. J Am Coll Cardiol. 2008;52:1527–39.
2. Ronco C, McCullough P, Anker SD, et al., Acute Dialysis Quality Initiative (ADQI) Consensus Group. Cardio-renal syndromes: report from the consensus conference of the Acute Dialysis Quality Initiative. Eur Heart J. 2010;31:703–11.
3. Valika AA, Costanzo MR. The acute cardiorenal syndrome type I: considerations on physiology, epidemiology, and therapy. Curr Heart Fail Rep. 2014;11:382–92.
4. Krüger W. Acute heart failure. Putting the puzzle of pathophysiology and evidence together in daily practice. 2nd ed. Switzerland: Springer International Publishing AG; 2017. p. 371–400.
5. Ezekowitz JA, O'Meara E, McDonald MA, et al. 2017 comprehensive update of the Canadian Cardiovascular Society guidelines for the management of heart failure. Can J Cardiol. 2017;33:1342–433.
6. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37:2129–200. Erratum in: Eur Heart J. 2016 Dec 30.
7. Sica DA. Edema mechanisms in the heart failure patient and treatment options. In: Bakris GL, editor. Managing the kidney when the heart is failing. New York: Springer Science; 2012. p. 73–89.
8. Pease J. Acute decompensated heart failure in the observation unit: treatment protocols. In: Peacock WF, editor. Short stay management of acute heart failure. 3rd ed. Switzer-

land: Humana Press Springer International Publishing; 2017. p. 197–210 [Contemporary Cardiology].
9. Martins JL, Santos L, Faustino A, et al. Worsening or 'pseudo-worsening' renal function? The prognostic value of hemoconcentration in patients admitted with acute heart failure. Rev Port Cardiol. 2018;37:595–602.
10. Testani JM, Brisco MA, Chen J, et al. Timing of hemoconcentration during treatment of acute decompensated heart failure and subsequent survival: importance of sustained decongestion. J Am Coll Cardiol. 2013;62:516–24.
11. Oh J, Kang SM, Hong N, et al. Hemoconcentration is a good prognostic predictor for clinical outcomes in acute heart failure: data from the Korean Heart Failure (KorHF) Registry. Int J Cardiol. 2013;168:4739–43.
12. Vaduganathan M, Greene SJ, Fonarow GC, et al. Hemoconcentration-guided diuresis in heart failure. Am J Med. 2014;127:1154–9.
13. Darawsha W, Chirmicci S, Solomonica A, et al. Discordance between hemoconcentration and clinical assessment of decongestion in acute heart failure. J Card Fail. 2016;22:680–8.
14. Zhou H, Xu T, Huang Y, et al. The top tertile of hematocrit change during hospitalization is associated with lower risk of mortality in acute heart failure patients. BMC Cardiovasc Disord. 2017;17:235.
15. Davila C, Reyentovich A, Katz SD. Clinical correlates of hemoconcentration during hospitalization for acute decompensated heart failure. J Card Fail. 2011;17:1018–22.
16. van der Meer P, Postmus D, Ponikowski P, et al. The predictive value of short-term changes in hemoglobin concentration in patients presenting with acute decompensated heart failure. J Am Coll Cardiol. 2013;61:1973–81.